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<p>(54) Title: COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS CONTAINING BISMUTH AND NSAID</p> <p>(57) Abstract</p> <p>The present invention relates to methods and compositions for treating a gastrointestinal disorder caused or mediated by <i>Helicobacter pylori</i> comprising bismuth, and a gastropathic amount of a non-steroidal anti-inflammatory drug. The inventions may further comprise therapeutically effective amounts of one or more anti-secretory drugs.</p>		

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COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS CONTAINING BISMUTH AND NSAID

BACKGROUND OF THE INVENTION

10 Upper abdominal pain and other gastrointestinal disorders are common and chronic problems for a vast number of the population. Of the individuals examined and diagnosed by their physicians, many can be shown to have diseases such as peptic or other ulcers, or non-ulcer dyspepsia. Until the mid 1980s, these conditions were thought to be caused by stress, diet or other environmental factors. Research now
15 indicates that *Helicobacter pylori*, (hereinafter referred to as "*H. pylori*") a bacterium found exclusively in the gastric mucus of humans, plays a major role in the pathogenesis of these diseases and other gastrointestinal disorders.

Various methods and agents have been used to treat and/or eradicate gastrointestinal disorders caused by *H. pylori*. These include the administration of
20 antacids, H₂ antagonists, and antimicrobials such as antibiotics. In addition, speculation on the benefits of other methods for treating *H. pylori* is also available in the art. An example of such is found in Tanaka, S., et al., "Gastroprotective Effect of Ranitidine Bismuth Citrate Is Associated With Increased Mucus Bismuth Concentration In Rats", Gut, 39:164-171 (1996). However, given the prevalence and incidence of infection with
25 *H. pylori*, the difficulty in treating many patients suffering from such gastrointestinal disorders caused or mediated by *H. pylori*, and the potential for resistance with antibiotic-containing regimens, a continuing need exists for safe and effective treatments against *H. pylori*, preferably which would be effective as mass treatment therapies in large populations of *H. pylori* carriers.

30 Compositions and methods have been discovered by the present invention for the treatment of gastrointestinal disorders caused or mediated by *H. pylori* comprising the administration of bismuth salts, (other than salts formed between an H₂ receptor antagonist and a complex of bismuth with a carboxylic acid), and a non-steroidal anti-inflammatory drug. The present invention also comprises the optional administration of
35 one or more antisecretory agents. It is believed that the administration of bismuth with a non-steroidal anti-inflammatory drug enhances gastric mucus bismuth concentrations.

Thus, an object of the present invention is to provide safe and effective compositions and methods of treating gastrointestinal disorders caused or mediated by *H. pylori*.

SUMMARY OF THE INVENTION

5 The present invention relates to a composition for treating a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising from about 50 milligrams to about 5000 milligrams, per day, of bismuth; a gastropathic amount of a non-steroidal anti-inflammatory drug; and pharmaceutically acceptable carriers.

10 The present invention also relates to a method for treatment of a human or lower animal subject having a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising administering to the subject from about 50 milligrams to about 5000 milligrams of bismuth, per day, for from about 1 to about 42 days, and a gastropathic amount of a non-steroidal anti-inflammatory drug.

DETAILED DESCRIPTION OF THE INVENTION

15 The present invention relates to methods and compositions comprising bismuth and a non-steroidal anti-inflammatory drug for treating a gastrointestinal disorder caused or mediated by *Helicobacter pylori*. The inventions may optionally comprise therapeutically effective amounts of one or more antisecretory agents. The compositions also comprise pharmaceutically acceptable carriers. The present invention and the
20 essential and optional components therein are described fully below.

Helicobacter pylori

H. pylori are spiral bacteria which reside in the stomach. When first identified in the early 1980s, *H. pylori* was referred to by the name *Campylobacter pyloridis*. In recent years, these bacteria have been implicated as a causative factor for gastritis, non-
25 ulcerative dyspepsia, and various ulcers of the gastrointestinal tract. These organisms are described in detail in the following publications, all of which are incorporated herein by reference in their entireties: Korman, M.G., Tygat, G.N., "*Helicobacter pylori* and Peptic Ulcer", Scandinavian Journal of Gastroenterology, Suppl., 210:92-96 (1995); Marshall, B. J., "*Helicobacter pylori*", American Journal of Gastroenterology, 89(8
30 Suppl):S116-128 (Aug. 1994); Calam, J., "*Helicobacter pylori*", European Clinical Investigation, 24(8):501-510 (Aug. 1994); NIH Consensus Conference, "*Helicobacter pylori* in Peptic Ulcer Disease. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease", JAMA, 272(1):65-69 (July 6, 1994); and Marshall, B. J., Warren, J. R., "Unidentified Curved Bacilli in the Stomach of Patients with Gastritis and Peptic Ulceration", The Lancet, 1311-1315 (1984).

Gastrointestinal Disorder

The term "gastrointestinal disorder", as used herein, encompasses any infection, disease or other disorder of the body, typically of the upper and/or lower gastrointestinal tract, caused or mediated by *H. pylori*. An individual having such a gastrointestinal disorder may be symptomatic or asymptomatic. Such disorders include, for example, *H. pylori* disorders not manifested by the presence of ulcerations in the gastric mucosa, including chronic active or atrophic gastritis, non-ulcer dyspepsia, esophageal reflux disease and gastric motility disorders; and peptic ulcer disease, i.e., *H. pylori*-mediated pre-pyloric, marginal, gastric, duodenal and/or jejunal ulcers.

In the present invention, the presence of a gastrointestinal disorder caused or mediated by *H. pylori* is preferably determined by any of the diagnostic methods recognized and utilized by the medical community. Details concerning such methods are described more fully in the following publications, all of which are incorporated herein by reference in their entireties: Megraud, F., "Diagnosis of *Helicobacter pylori* Infection", Scandinavian Journal of Gastroenterology, Supplement, 214: 44-46, 57-60 (1996); Cutler, A. F., "Testing for *Helicobacter pylori* In Clinical Practice", American Journal of Medicine, 100(5A): 35S-39S, 39S-41S (May 20, 1996); Megraud, F., "Diagnosis of *Helicobacter pylori*", Baillieres Clinical Gastroenterology, 9(3): 507-518 (Sept. 1995); and Feldman, R. A., et al., "Accuracy of Diagnostic Methods Used for Epidemiological Studies of *Helicobacter pylori*", Alimentary Pharmacology and Therapeutics, 9 Suppl. 2:21-31 (1995).

Bismuth

The present invention involves administration of bismuth. As used herein, the quantity of bismuth is by weight of elemental bismuth.

In the present inventions, bismuth may be in the form of a pharmaceutically-acceptable salt, or may be in the form of an organic complex which contains bismuth as an active ingredient. Such organic complexes include 2,2'-spirobi[1,3,2-benzodioxabismole]. Salts formed between an H₂ receptor antagonist and a complex of bismuth with a carboxylic acid are not included for use in the present inventions. Preferably, bismuth is administered in the present methods as a pharmaceutically-acceptable salt. Such bismuth salts include bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrate bismuthate, bismuth subgallate, bismuth subnitrate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof. Bismuth citrate, bismuth subcitrate, tripotassium dicitrate bismuthate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof are preferred bismuth salts for use in this invention.

The bismuth useful herein may be administered alone, or in combination with other pharmaceutically-acceptable components in a bismuth-containing composition. A

variety of such compositions containing bismuth salts are commercially available. Such compositions include DeNol, containing tripotassium dicitrato bismuthate (by Brocades); Bislumina, containing bismuth aluminate (by Mazuelos); Roter, containing bismuth subnitrate (by Roterpharma); Devrom®, containing bismuth subgallate (by The Parthenon Co., Inc.); and Pepto-Bismol®, containing bismuth subsalicylate (by The Procter & Gamble Company).

In general, bismuth may be administered in an amount of from about 50 milligrams to about 5000 milligrams per day, and preferably from about 50 milligrams to about 2500 milligrams, per day, for from about 1 to about 42 days, preferably for up to about 28 days, and most preferably for up to about 14 days.

Non-Steroidal Anti-Inflammatory Drugs

The present invention comprises the administration of bismuth with a non-steroidal anti-inflammatory drug ("NSAID"). The term "NSAID", as used herein, refers to any agent which has anti-inflammatory, antipyretic and analgesic properties. Examples of NSAIDs are described in U.S. Patent 4,985,459 to Sunshine et al., issued January 15, 1991, incorporated by reference herein in its entirety. For detailed disclosure of the chemical structure, synthesis, side effects, etc. of non-steroidal anti-inflammatory agents, references may be had to standard texts, including Anti-Inflammatory and Anti-Rheumatic Drugs, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton (1985), and Anti-Inflammatory Agents, Chemistry and Pharmacology, I R. A. Scherrer, et al., Academic Press, New York (1974), both of which are incorporated by reference herein.

Specific NSAIDs useful in the present invention include, but are not limited to: the oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam, and CP-14,304; the salicylates, such as acetylsalicylic acid, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal; the acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepiract, clidanac, oxepinac, and felbinac; the fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids; the propionic acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic; and the pyrazoles, such as phenylbutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone. Mixtures of these NSAIDs may also be employed, as well as the pharmaceutically-acceptable salts and esters of these agents.

Another class of NSAIDs are disclosed in U.S. Patent No. 4,708,966, Loomans, et al., issued November 24, 1987. This patent discloses a class of non-steroidal anti-

inflammatory compounds which comprise specifically substituted phenyl compounds, especially substituted 2,6-di-tert-butyl phenol derivatives. For example, compounds selected from 4-(4'-pentyn-3'-one)-2,6-di-*t*-butylphenol; 4-(5'-hexynoyl)-2,6-di-*t*-butylphenol; 4-((S)-(-)-3'-methyl-5'-hexynoyl)-2,6-di-*t*-butylphenol; 4-((R)-(+)-3'-methyl-5'-hexynoyl)-2,6-di-*t*-butylphenol; and 4-(3',3'-dimethoxypropionyl)-2,6-di-*t*-butylphenol are useful in the present invention.

Examples of preferred NSAIDs useful in the present invention include, but are not limited to: acetylsalicylic acid, ibuprofen, fenbuprofen, fenoprofen, flurbiprofen, indomethacin, ketoprofen, naproxen, their pharmaceutically-acceptable salts, enantiomers thereof, and mixtures thereof. Ibuprofen, indomethacin, acetylsalicylic acid, and naproxen are especially preferred for use in the present invention.

NSAIDs are administered in a gastropathic amount. The term "gastropathic amount", as used herein, refers to a level and frequency of administration of NSAID which is sufficient to produce gastropathy, e.g. mucosal damage as judged by fiberoptic endoscopy, in normal subjects after a one week course of therapy. Such an amount will vary depending on the particular NSAID being administered, the size and/or condition of the subject receiving treatment and/or other medical factors determined by the administering physician. The gastropathic amounts for specific NSAIDs are known in the art. For example, acetylsalicylic acid administered at a levels of about 2.4 to 3.9 grams per day for one week will consistently produce mucosal injury without causing complications. Gastropathic amounts for other NSAIDs are levels which produce comparable gastropathy to the gastropathy produced by the acetylsalicylic acid levels disclosed herein.

The following publications provide greater detail on gastropathy and NSAIDs, and are incorporated herein by reference in their entireties: Heigh, R. I., "Use of NSAIDs. An Assault on the Upper Gastrointestinal Tract", Postgraduate Medicine, 96(6):63-68 (Nov. 1, 1996); Levi, S., et al., "Non-Steroidal Anti-Inflammatory Drugs: How Do They Damage the Gut?", British Journal of Rheumatology, 33(7):605-612 (July 1994); and Bower, P. R., "Non-Steroidal Anti-Inflammatory Drugs", British Journal of Rheumatology, 32 Suppl. 4:35-38 (June 1993).

In the present invention, the duration of NSAID administration is for up to about 14 days, and preferably for from 1 about to about 10 days. The duration of administration should be less than that associated with the development of complications. Therefore, the most preferred duration of administration of the NSAID is from about 1 to about 7 days. In addition to the publications mentioned in the preceding paragraph, complications associated with NSAID usage are discussed in Fenn, G. C., "Review Article: Controversies in NSAID-induced Gastroduodenal

Damage--Do They Matter?", Alimentary Pharmacology and Therapeutics, 8(1):15-26 (Feb. 1994), incorporated herein by reference in its entirety.

Antisecretory Agents

The present invention can optionally include one or more antisecretory agents.

5 The term "antisecretory agent", as used herein, refers to agents selected from the group consisting of H₂ receptor antagonists, proton pump inhibitors, and mixtures thereof. These agents are administered in a therapeutically effective amount. The term "therapeutically effective amount", as used herein, refers to a level which is commonly known in the art and recognized and utilized by the medical community. Such an

10 amount will vary depending on the particular agent(s) administered, the size and/or condition of the individual receiving treatment or other medical factors determined by the administering physician.

H₂ receptor antagonists are disclosed fully in U.S. Patent No. 5,294,433 to Singer et al., issued March 15, 1994, incorporated herein by reference in its entirety.

15 Preferred H₂ receptor antagonists include cimetidine, etintidine, ranitidine, ICIA-5165, tiotidine, ORF-17578, luptidine, donetidine, famotidine, roxatidine, pifatidine, lamtidine, BL-6548, BMY-25271, zaltidine, nizatidine, mifentidine, BMY-52368, SKF-94482, BL-6341A, ICI-162846, ramixotidine, Wy-45727, SR-58042, BMY-25405, loxidine, DA-4634, bisfentidine, sufotidine, ebrotidine, HE-30-256, D-16637, FRG-

20 8813, FRG-8701, impromidine, L-643728, HB-4-08, and mixtures thereof.

Preferred for use in the present invention are cimetidine, ranitidine, famotidine, roxatidine, nizatidine, mifentidine, and mixtures thereof. Most preferred are cimetidine and ranitidine.

Proton pump inhibitors are described in greater detail in the following

25 publications, which are incorporated by reference herein in their entireties: U.S. Patent No. 4,786,505 to Lovgren, issued November 22, 1988; U. S. Patent No. 4,255,431 to Junggren, issued March 10, 1981; and U.S. Patent No. 4,853,230 to Lovgren, issued August 1, 1989. Preferred for use in the present invention are omeprazole, lansoprazole, pantoprazole, and mixtures thereof. Most preferred is omeprazole.

30 Antisecretory agents may be administered for from about 1 to about 42 days, preferably for up to about 28 days, and most preferably for up to about 14 days.

Pharmaceutically Acceptable Carriers

The compositions of the present invention may contain optional components which affect the physical and therapeutic characteristics of the present compositions. In

35 particular, a variety of pharmaceutically-acceptable carriers and excipients may be included, depending upon the particular dosage form to be used. Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk

powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions, and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring, and flavoring agents.

Specific examples of pharmaceutically-acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U. S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein. Techniques and compositions for making dosage forms useful herein are described in the following references, all incorporated by reference herein: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker and Rhodes, editors, 1979); an Lieberman, et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms (2d edition, 1976).

The compositions of this invention may be used according to the methods of this invention by administering the composition from 1 to 4 times per day, and preferably from 1 to 2 times per day; for from 1 to 28 days, preferably for from about 1 to about 21 days, and most preferably for from about 1 to about 14 days. The specific frequency of administration will depend upon such factors as the specific NSAID, bismuth compound or composition and antimicrobial(s) used, the levels at which the components are incorporated in the composition, the nature and severity of the condition to be treated, and the nature of any concurrent therapy, if any.

Method of Use

The methods of the present invention comprise the treatment of a human or lower animal subject having a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising administering to the subject bismuth and a non-steroidal anti-inflammatory drug (hereinafter referred to as "NSAID"). The present method may further comprise the administration of one or more antisecretory agents.

As used herein, the term "administering" refers to any method which, in sound medical practice delivers the compounds or compositions used in this invention to the subject to be treated in such a manner so as to be effective in the treatment of the gastrointestinal disorder. Preferably, the bismuth, NSAID, and antisecretory agent(s), if present, are administered orally.

The present invention encompasses methods wherein the administering of bismuth, the NSAID, and optionally the antisecretory agent(s) are performed

simultaneously (beginning and ending on the same day), concurrently (overlapping but not of the same duration of administration), or consecutively (sequential, but where the course of treatment is substantially continuous). Preferably, the bismuth and NSAID are administered concurrently and administration for both bismuth and the NSAID is commenced on the same day. Additionally, if one or more antisecretory agents are also present, it is preferred that the bismuth and the antisecretory agent(s) are administered simultaneously.

The following non-limiting examples illustrate the composition and methods of use of the present invention.

EXAMPLE I

An asymptomatic young volunteer identified as having *H. pylori* infection through the results of a mass screening, is treated by a method of the present invention. The subject is orally administered approximately 2500 milligrams of bismuth in the form of bismuth subsalicylate daily, (sold by The Procter & Gamble Company under the name "Pepto-Bismol®"), in four equal doses, for 28 days; and approximately 100-200 milligrams of indomethacin daily, in four equal doses, for about 14 days. One to two months later, a diagnostic test performed on the volunteer shows no evidence of *H. pylori*.

In the above example, tripotassium dicitrato bismuthate, bismuth tartrate, bismuth citrate, and bismuth subnitrate are substituted, respectively, for bismuth subsalicylate, with substantially similar results.

EXAMPLE II

A human subject is suffering from chronic active gastritis. A diagnostic test reveals the presence of *H. pylori*. The individual is treated by orally administering approximately 500 milligrams of bismuth daily in the form of bismuth subcitrate ("DeNol", sold by Brocades), in two equal doses, for about 28 days; approximately 3.9 grams of acetylsalicylic acid daily, in three equal doses, for about 14 days; and approximately 20 milligrams of omeprazole daily, for 28 days. Administration of all three agents is commenced on the same day. One to two months later, the diagnostic test is repeated. The results show no evidence of *H. pylori*.

EXAMPLE III

A human subject is suffering from non-ulcer dyspepsia. A biopsy of the gastric mucosa is taken from the stomach of the subject. Analysis of the biopsy sample indicates the presence of urease in the sample and the presence of *H. pylori* in the stomach of the subject. The subject is given approximately 1200 milligrams of bismuth daily, (administered as bismuth subsalicylate in the composition Pepto-Bismol®, sold by The Procter & Gamble Company), in four equal doses, for about 21 days; 1200-3200

milligrams of ibuprofen daily, in three to four equal doses, for about 7 days; and 150 milligrams of ranitidine daily, in two equal doses, for about 21 days. Administration of all three agents is commenced on the same day. A biopsy sample taken and analyzed one to two months later shows no evidence of *H. pylori*.

WHAT IS CLAIMED IS:

1. A composition for treating a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising:
 - a) from 50 milligrams to 5000 milligrams, per day, of bismuth;
 - b) a gastropathic amount of a non-steroidal anti-inflammatory drug; and
 - c) pharmaceutically acceptable carriers.
2. The composition of Claim 1 further comprising a therapeutically effective amount of one or more antisecretory agents selected from the group consisting of H₂ receptor antagonists, proton pump inhibitors and mixtures thereof.
3. The composition of Claim 1 or 2 wherein the antisecretory agents are selected from the group consisting of cimetidine, ranitidine, famotidine, roxatidine, nizatidine, mifentidine, omeprazole, lansoprazole, pantoprazole, and mixtures thereof.
4. The composition of any of Claims 1-3 wherein the bismuth is selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrate bismuthate, bismuth subgallate, bismuth subsalicylate, bismuth tartrate, and mixtures thereof and is administered at a level of from 50 milligrams to 2500 milligrams, per day for 7 to 28 days.
5. The composition of any of Claims 1-4 wherein the non-steroidal anti-inflammatory drug is selected from the group consisting of ibuprofen, indomethacin, acetylsalicylic acid, and naproxen and wherein it is administered for up to 14 days, and the one or more antisecretory agents are administered for 7 to 28 days.
6. The use of the compositions of any of Claims 1-5 for the manufacture of a composition for treatment of a human or lower animal subject having a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising administering to the subject from 50 milligrams to 5000 milligrams of bismuth, per day, for from 1 to 42 days and a gastropathic amount of a non-steroidal anti-inflammatory drugs for up to 14 days.

7. The use of the compositions of any of Claims 1-6 for the manufacture of a composition comprising a therapeutically effective amount of one or more antisecretory agents which are selected from the group consisting of H₂ receptor antagonists, proton pump inhibitors and mixtures thereof.
8. The use of the compositions of any of Claims 1-7 for the manufacture of a composition wherein the bismuth is selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrate bismuthate, bismuth subgallate, bismuth subsalicylate, bismuth tartrate, and mixtures thereof and is administered at a level of from 50 milligrams to 2500 milligrams, per day for 7 to 28 days.
9. The use of the compositions of any of Claims 1-8 for the manufacture of a composition wherein the non-steroidal anti-inflammatory drug is selected from the group consisting of ibuprofen, indomethacin, acetylsalicylic acid, and naproxen and the antisecretory agents are selected from the group consisting of cimetidine, ranitidine, famotidine, roxatidine, nizatidine, mifentidine, omeprazole, lansoprazole, pantoprazole, and mixtures thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/21462

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K33/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 262 036 A (GLAXO GROUP LTD) 9 June 1993 see abstract	1-9
X	TANAKA S ET AL: "Indomethacin increases mucus bismuth concentration in ranitidine bismuth citrate treated rats" GASTROENTEROLOGY, 108 (4 SUPPL.). 1995. A234., XP002059838 see the whole document	1,4,5
X	EP 0 437 294 A (GIST BROCADES NV) 17 July 1991 see page 3, line 18-24	1,4
X	WO 93 09784 A (PROCTER & GAMBLE) 27 May 1993 see page 5, line 27-31	1,4

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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